

Febrile Neutropaenia in Cancer Patients

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ABSTRACT

Backgrounds: Febrile neutropaenia is a common complication of chemotherapy in cancer patients. Empirical antibiotic regimes are based on the epidemiological characteristics of bacterial isolates globally and locally.

Method: This study retrospectively reviewed all cases of febrile neutropaenia in patients with confirmed cancer admitted at the University Hospital of the West Indies in the four-year period between, January 1, 2003 and December 31, 2006 and who received chemotherapy. Cases were identified from blood culture records and hospital charts which were reviewed to determine the aetiological agents causing bacteraemia, their antimicrobial susceptibilities and clinical features. These cases were compared with non-neutropaenic cancer patients admitted with fever.

Results: A total of 197 febrile episodes in cancer patients were reviewed. Thirty-seven per cent had febrile neutropaenia while 62% were non-neutropaenic. Acute myeloid leukaemia was the most common haematological malignancy and the most common solid tumour was breast cancer. Twenty-six per cent of patients had a positive blood culture.

In febrile neutropaenic patients, *Escherichia coli* was the most common organism isolated followed by coagulase-negative staphylococci while in non-neutropaenic patients, coagulase-negative staphylococci was most common. *Acinetobacter* infections was prominent in non-neutropaenic patients but absent in neutropaenic patients. More than one organism was cultured in 9 neutropaenic and 18 non-neutropaenic patients. Mortality was 10.8% in neutropaenic and 24.4% in non-neutropaenic patients.

Conclusion: Gram-negative organisms are the predominant isolates in febrile neutropaenic episodes in this cohort of patients. Non-neutropaenic patients had an increased mortality with an increase in *Acinetobacter* infections and multiple isolates.

Keywords: Cancer, febrile neutropaenia

Neutropenia Febril en Pacientes con Cáncer

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RESUMEN

Antecedentes: La neutropenia febril es una complicación común de la quimioterapia en pacientes con cáncer. Los regímenes de antibióticos empíricos se basan en las características epidemiológicas de aislados bacterianos, tanto global como localmente.

Método: Este estudio examinó retrospectivamente todos los casos de neutropenia febril con confirmación de cáncer, ingresados y tratados con quimioterapia en el Hospital Universitario de West Indies, Jamaica, en el período de cuatro años entre el 1ero, de enero de 2003 y el 31 de diciembre de 2006. Se identificaron casos con historias de cultivos de sangre e historias clínicas que fueron examinadas para determinar los agentes etiológicos causantes de la bacteriemia, sus susceptibilidades antimicrobianas y características clínicas. Estos casos fueron comparados con pacientes de cáncer no neutropénicos ingresados con fiebre.

Resultados: Se examinaron un total de 197 episodios febriles en pacientes de cáncer. El treinta y siete por ciento tuvo neutropenia febril, mientras que el 62% eran no neutropénicos. La leucemia mieloide aguda fue la malignidad hematológica más común, y el tumor sólido más común fue el cáncer de mamas. Veintiséis por ciento de los pacientes tuvieron cultivos de sangre positivos. En los pacientes

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neutropénicos febriles, Escherichia coli fue el organismo aislado más común, seguido de los estafilococos coagulasa-negativos, mientras que en los pacientes no neutropénicos, los estafilococos coagulasa-negativos fueron los más comunes. Las infecciones por Acinetobacter fueron prominentes en pacientes no neutropénicos pero ausentes en los pacientes neutropénicos. Más de un organismo fue cultivado en 9 pacientes neutropénicos y 18 en no neutropénicos. La mortalidad fue de 10.8% en los pacientes neutropénicos y 24.4% en los no neutropénicos.

Conclusión: *Los organismos gram-negativos son los aislados que predominan en los episodios neutropénicos febriles en Jamaica. Los pacientes no neutropénicos vieron su mortalidad aumentada con el incremento en infecciones Acinetobacter y aislados múltiples.*

Palabras claves: cáncer, febril neutropenia

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INTRODUCTION

Cancer is a leading cause of death in most countries. In Jamaica, the Cancer Registry reports that the age standardized rates per 100 000 for cancers in males was 188.6 and in females 144.2 (1). Importantly, cancer-related deaths in Jamaicans account for 16% of all deaths (2).

Chemotherapy is a key component in the management of both solid tumours and haematological malignancies. However, treatment may be complicated by haemorrhage and infection. Infection caused 36% mortality in neutropaenic and 31% in non-neutropaenic patients (3).

The incidence of infection is high in cancer patients on chemotherapy since this may result in a neutropaenic state. Cancer-induced neutropaenia (CIN) is more likely to be complicated by bacterial infection, the longer the duration of neutropaenia and the greater the severity of the neutropaenia (3). An episode of febrile neutropaenia, with temperature of greater than 38°C for at least one hour and neutropaenia with less than 1000 cells/mm³ with expected fall to less than 500 cells/mm³, represents a bacterial infection in over 50% of cases.

The cornerstone of treatment of patients with febrile neutropaenia is the use of empirical antibiotic regimes. These are based on the likely organisms and their resistance patterns. The majority of infections in neutropaenic patients are usually caused by micro-organisms of the patient's own endogenous flora, including both gram-positive and gram-negative organisms. Since the early 1990s, most cancer centres have experienced a change in the most common isolated organisms from gram-negative to gram-positive organisms (4). In developed countries, gram-positive organisms predominate (5, 6). However, data from developing countries including the Middle East and South America still report a predominance of gram-negative bacteraemia in this patient population (7–10). Knowledge of the aetiological agents is central to selection of initial empirical antibiotic regimes. Therefore, frequent surveillance is important because institutional and country differences are often substantial and most available guidelines are based on national data from the United States of America (USA) and Europe.

There have been no published data from the Caribbean on the aetiological pattern of organisms seen in patients with

febrile neutropaenia. Therefore, it is unknown how effective the adoption of the Infectious Diseases Society of America (IDSA) guidelines (11) is in management of these patients or whether a different protocol should be developed for Caribbean patients. This is also important as the Caribbean is a developing region with limited resources and the standard of care recommended in international guidelines is expensive and labour-intensive.

This study examined the aetiology and sensitivity patterns of bacterial infections in febrile neutropaenic patients at the University Hospital of the West Indies (UHWI), Jamaica. It also determined whether infections in chemotherapy-induced neutropaenic patients is similar to cancer patients who are not neutropaenic.

SUBJECTS AND METHODS

All cases of febrile neutropaenia in patients with confirmed cancer and who received chemotherapy and were admitted to the UHWI in the four-year period between January 1, 2003 and December 31, 2006 were reviewed. Cases were identified from blood culture records of the Department of Microbiology where patients with the diagnoses: cancer and sepsis, cancer with fever and febrile neutropaenia were selected. The medical records of these patients were reviewed to include only cases of febrile neutropaenia. Cases with confirmed febrile neutropaenia that were included were defined by IDSA criteria, with single oral temperature greater than 38.3°C or a temperature exceeding 38°C for more than one hour, with absolute neutrophil count (ANC) less than 500 cells/mm³ or less than 1000 cells/mm³ with expected nadir of less than 500 cells/mm³. Cases with febrile neutropaenic episodes not associated with malignancy or chemotherapy were excluded.

Patients with cancer without chemotherapy-induced neutropaenia who were admitted for sepsis were also included for comparison of the causative agents of sepsis with the febrile neutropaenic patients. These cases were admitted to the UHWI during the same period, January 1, 2003 to December 31, 2006.

The medical records for all patients were reviewed and the following data obtained; age, gender, presenting symptoms, signs and the clinical sites of infection. In addition, the

type of cancer, chemotherapeutic agents given and administration of granulocyte colony-stimulating factor (G-CSF) were also documented. Also, positive culture results and sensitivity, complete treatment administered including antibiotic prophylaxis, empirical antibiotics and subsequent change in antibiotic regimes and outcomes were documented

Blood cultures obtained from patients were processed by the UHWI Microbiology laboratory using the automated Bactec 9240 blood culture system. Gram-negative isolates were identified using the automated VITEK system (bio Merieux) and Gram-positive isolates were identified manually based on morphology and biochemical tests. Antibiotic susceptibility testing was performed using a combination of the modified Kirby-Bauer disk diffusion method based on CLSI guidelines and the automated VITEK system.

Data management and statistical analysis was accomplished using version 12.0 of the Statistical Package for the Social Sciences (SPSS, Inc, Chicago, IL, USA) and Microsoft Excel 2003 software. Descriptive statistics, including frequencies and valid percentages, were computed following the appropriate computation of specifically required variables from existing information utilizing SPSS syntax. Cross-tabulations were also done on variables with categorical levels to explore occurrences bivariately and relevant percentages were evaluated using the Chi-squared test of homogeneity of these proportions within such contingency tables. Logistic regression analysis was also employed to assess both bivariate and multivariate relationships expressed as odds ratios where the dependent variable was dichotomous. However, where the dependent variable was continuous and adequately approximated, a normal distribution potential difference between levels of grouping variables of interest (*eg*, gender *etc.*) was assessed using the independent groups *t*-test. The critical probability value used in assessing the statistical significance of hypotheses tested here was chosen to be $p = 0.05$ in this study.

RESULTS

Between 2002 and 2006, a total of 197 patient febrile episodes were reviewed in patients hospitalised with cancer and fever on the medical (adult and paediatric) wards. There were 123 (62%) non-neutropaenic patients and 74 (37%) had chemotherapy-induced neutropaenia (CIN). The age range was 2–91 years, the mean age of non-neutropaenic patients was 51 years and neutropaenic patients 40 years. Fifty-two per cent of the total number was female and 48% male. There was no significant difference between gender and neutropaenia, with 40% females and 35% males being neutropaenic. The most common malignancies were haematological with acute myeloid leukaemia being the most common, accounting for 18% (Table 1). The most common solid tumour malignancy was breast cancer. There was no significant difference in the type of cancer and the association with CIN except colon cancer, unknown primary and myeloma, which were predominantly non-neutropaenic.

Table 1: Types of cancer

Cancer	Number
Acute leukaemias	51
Chronic leukaemias	7
Acute T cell lymphoma	23
Non-Hodgkins lymphoma	22
Hodgkins lymphoma	11
Myeloma	16
Breast	17
Lung	6
Gastrointestinal	15
Gynaecological	4
Genitourinary	3
Others	10
Primary unknown	5

Most patients presented with fever alone. Lower respiratory tract infections were the most common source of infection identified, occurring in twenty-seven (22%) non-neutropaenic cases and nine (12%) CIN cases (Table 2).

Table 2: Presenting symptoms and signs

Presenting symptoms and signs	ALL patients	CIN	Non-neutropaenic
Fever only	127	51	76
LRTI	37	10	27
UTI	6	2	4
Skin sepsis	6	3	3
Sore throat	5	4	1
Altered mental State	4	0	4
Abdominal pain,	10	3	7
Diarrhoea, vomiting			
Weight loss	1	0	1
URTI	1	1	0
Ear infection	1	0	1

Overall, 26% of patients had a positive blood culture. There was no significant difference between non-neutropaenic (27%) and CIN (24%) patients with respect to blood culture yield. Additional cultures from different sources were taken depending on the clinical symptoms at presentation and the yield from all sources improved from 26% to 40%. There was no significant difference between non-neutropaenic patients with a positive culture in 41% cases and CIN patients with positive culture in 37% of cases. In most cases, only a single organism was isolated, but more than one organism was cultured in 9 CIN patients and 18 non-neutropaenic patients. The most common organism isolated overall was coagulase-negative staphylococci (Table 3). However, in CIN patients, the most common organism isolated was *Escherichia coli* followed by coagulase negative staphylococcus. *Pseudomonas aeruginosa* was the second most common organism isolated in non-neutropaenic pa-

Table 3: Gram-Positive organisms isolated.

Gram-Positive Organisms	ALL	CIN	Non-Neutropaenic
Coagulase-Negative Staphylococcus	19	7	2
Gp D Streptococcus	12	4	8
S aureus	10	1	9
Strep. viridans	4	2	2
Strep. pneumoniae	2	0	2
Beta-haemolytic Streptococcus	1	0	1
Staph citreus	1	0	1

tients (Table 4). There were no fungal infections in either group.

Table 4: Gram-Negative organisms isolated.

Gram-Negative Organisms	ALL	CIN	Non-Neutropaenic
Escherichia coli	15	8	7
Pseudomonas aeruginosa	14	4	10
Acinetobacter	9	0	9
Klebsiella spp	8	5	3
S maltophilia	5	2	3
Enterobacter spp	4	2	2
Salmonella	1	0	1
Serratia	1	0	1
H influenza	1	1	0

Amoxicillin/clavulanate, gentamicin, ceftazidime and piperacillin/tazobactam were the most commonly administered antibiotics overall. In CIN patients, gentamicin in combination with another antibiotic was the most commonly used antibiotic followed by amoxicillin/clavulanate, ceftazidime and ceftriaxone. Ceftazidime and gentamicin were used in combination in 32% of CIN cases and only 15% non-neutropaenic patients ($p = 0.005$). The use of the combination of amoxicillin/clavulanate and ciprofloxacin was similar between the two patient groups: 23% of CIN cases and 20% non-neutropaenic cases.

In total, 27% of patients were given antibiotics to which cultured organisms were sensitive. In patients with CIN, 75% survived, 32% were given appropriate antibiotics to which they were sensitive while 24% of non-neutropaenic patients were given the appropriate antibiotics (ns, $p = 0.105$).

Overall, 38 patients demised, 8 (11%) had CIN and 30 (24%) were non-neutropaenic. Of these patients, 34% received appropriate antibiotics. The appropriate antibiotics were administered in 25% of patients who survived. There was no statistical difference in the outcome of the patients when they were given the appropriate antibiotics ($p = 0.449$). Of the eight patients with CIN who died, five (63%) received

the appropriate antibiotics, while 29% who survived received antibiotics to which they were sensitive (ns, $p = 0.103$). Of the non-neutropaenic patients 24% (30/123) demised and of these, 27% received appropriate antibiotics. This is not statistically different from non-neutropaenic patients who as 23% received appropriate antibiotics.

Thirty-one patients (16%) were given granulocyte colony stimulating factor (G-CSF). Eighty per cent (25/31) of these patients were neutropaenic; 34% of CIN patients and 5% of non-neutropaenic patients were given G-CSF. All non-neutropaenic patients survived while 33% of CIN patients who survived were also given G-CSF. Of CIN patients who died, 38% had been given G-CSF. Overall, amongst those who died, 8% received G-CSF while 18% of those who survived received G-CSF.

DISCUSSION

Patients with CIN are at an increased risk of developing infection (12, 13). These infections are associated with increased morbidity, mortality and cost. Febrile neutropaenia is considered a medical emergency which requires hospitalization with prompt empirical antimicrobial therapy to improve outcomes (14, 15). The success of empirical antibiotic regimes is dependent on identifying epidemiological patterns globally as well as locally. At the UHWI, Jamaica, patients with febrile neutropaenia are initially managed with a third-generation cephalosporin and an aminoglycoside as first-line regimes based on IDSA guidelines (11). However, the ever changing patterns of infection, ecology and antibiotic resistance trends do not allow the development of treatment guidelines that can be applied universally (4).

The present review of febrile neutropaenia is comparable to other reports, however the 24% bacteraemia found in this study is slightly lower than in other studies (8, 10). In contrast to studies from developed countries with a predominance of gram-positive organisms, (4, 16) gram-negative organisms were most commonly isolated in the present study. Gram-negative organisms accounted for 57% of all identified isolates with *Escherichia coli* being the most common organism, accounting for 21%. These findings are in accordance with studies from other developing countries where gram-negative organisms are still the predominant isolates (7, 8). In Mexico, at least one pathogen was isolated in 35% of febrile neutropaenic episodes with *Escherichia coli* being isolated in 33% of isolates (8). In Taiwan, gram negative bacteria accounted for 57% of isolated pathogens and *Escherichia coli* was the most frequently isolated (9).

There are several factors that may account for the predominance of gram-negative organisms at this institution compared to developed countries. The use of long-term indwelling central catheters is practised widely in developed countries, which may serve as portals of entry for gram-positive skin commensals (17). The cost of placing these lines is prohibitive for the majority of patients. Also, the use of prophylactic antibiotics is limited by finance. Most

regimes used in developed countries target gram-negative organisms which allow the development of gram-positive colonisation. This was demonstrated with the development of streptococcal bacteraemia following the use of quinolone prophylaxis (18).

The findings, in the present study, differ from other studies where mono-microbial blood stream infections are the only infections described and infections from other sites are not included. In documented bacterial infections in patients with haematological malignancies and solid tumours, 23% and 31% respectively are polymicrobial (16). These infections are mainly tissue-based and associated with increased mortality. Significantly, 80% of these polymicrobial infections have an approximately 33% gram-negative component (19).

The non-neutropaenic arm of this study had findings consistent with other studies (20), with positive blood culture in 27% of cases and almost equal numbers of gram-positive and gram-negative organisms isolated. Coagulase-negative staphylococcus was the most common organism overall, accounting for 16%. Chemotherapy-induced neutropaenic patients are more susceptible to severe infections than non-neutropaenic cancer patients. The more severe infections occur with higher bacterial loads. Gram-negative bacteraemia tends to occur with higher bacterial loads than gram-positive bacteraemia (21). Thus more non-neutropaenic patients tend to have milder gram-positive infections than CIN patients.

International guidelines for recommended antibiotics in patients with febrile neutropaenia reflect the global trends of increasing gram-positive organisms but also give substantial gram-negative coverage. The IDSA guidelines recommend an aminoglycoside and an anti-pseudomonal cephalosporin, penicillin or imipenem and ciprofloxacin and amoxicillin-clavulanate for low-risk patients (11). In the index study, only 32% received ceftazidime and gentamicin and 23% received ciprofloxacin and amoxicillin-clavulanate. These two groups received the appropriate antibiotic in 32% of cases. Using this, the mortality rate was only 11% in this CIN group. This compares favourably with the 6.8% hospital mortality from a study in the United States of America (22). In this study, patients with febrile neutropaenia were not divided into risk groups, using clinical risk index scoring models developed for identifying low-risk CIN patients (3, 23). It is therefore possible that low-risk patients may have been included in this study. Currently, it is recognized that febrile neutropaenia represents a spectrum of potential severity and may run a benign course in some (23, 24).

There are no specific guidelines for empirical antibiotic regimes for non-neutropaenic cancer patients with sepsis. However, it is noted in this study that a similar number of non-neutropaenic patients who survived or died received appropriate antibiotics, thus other factors accounted for the mortality seen in this group. This group of non-neutropaenic

patients was older than the CIN patients and may have had an increased number of associated co-morbidities which were not analysed in this study. Also, *Acinetobacter* infections was prominent in this group but absent in CIN patients. *Acinetobacter* infections have been associated with increased mortality in cancer patients with sepsis (25). A recent comparative study of neutropaenic and non-neutropaenic patients revealed that non-neutropaenic patients tended to be older and to have a higher frequency of solid tumours and advanced or uncontrolled disease. *Acinetobacter* infections were also more frequent (20).

The limitations of this study include the lack of data on other factors that may influence the outcome of febrile neutropaenic patients including duration and severity of neutropaenia, cancer stage and activity, and comorbidities. The baseline pre-chemotherapy leucocyte counts was not recorded in this study and thus it is possible that ethnic benign neutropaenia may have been missed in some patients in the febrile neutropaenic group. However, chemotherapy is not usually started in patients with a total leucocyte count below 3.0×10^9 or neutrophil count below 1.5×10^9 .

Patients with febrile neutropaenia should be given the recommended antibiotics as delineated by IDSA guidelines (11). Empiric regimes need to be developed for non-neutropaenic patients. The factors that contribute to the high mortality in non-neutropaenic patients need to be identified and further investigated. This study confirms the need for regular local surveillance of epidemiological patterns of infections in patients with cancer in order to select the best, most economic empirical antibiotic therapy.

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